Mechanochemical endovenous ablation in the treatment of varicose veins

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DOI:
10.1053/j.semvascsurg.2015.02.002
10.1016/j.ejvs.2012.12.004
10.1016/j.jvsv.2014.01.001
10.1016/j.jvs.2012.07.049

Publication date:
2015

Chapter 1

Introduction and outline of the thesis

Varicose veins

History

Since the beginning of written history, mankind has suffered from varicose veins. Methods of treatment have been under development for more than 2000 years. The first description of varicose veins were found in the *Ebers papyrus*, over 3500 years ago[1]. This ancient Egyptian work described 'serpentine windings' which were not to be operated on because the patients would be 'head to the ground'. This is the first description of what must have been a failed attempt at surgery to treat varicose veins, implying that the use of incisions lead to fatal hemorrhage.

The first illustration of a varicose vein was found near the Enneakrounos fountain, at the foot of the Acropolis, Athens[2]. The sculpture dates back to the fourth century BC and was dedicated to Amynos, a physician. A patient is shown dedicating a large votive leg to Asclepius, the God of healing, in thanks for curing his varicose veins.

Figure 1.
Sculpture from the sanctuary of Amynos. End 4th century BC

The term 'varicose' is derived from the Latin word 'varix', which means twisted. It was probably used as a medical description by Hippocrates (460-377 BC). Hippocrates wrote some of the earliest medical descriptions of varicose veins. He confirmed that varicose veins were more frequent in Scythians due to the prolonged time spent on a horseback with legs hanging down. The *Hippocratic Treatises*, written in the first half of the 4th century BC, took treatment one step further and whilst he did not recommend the excision of varicose veins, he prescribed compression following multiple punctures. He also believed in cautery and is quoted as saying "what cannot be cured by medicaments is cured by the knife, what cannot be cured by the knife is cured by the searing iron, whatever this cannot cure must be considered incurable"[3].

Aurelius Cornelius Celsus (25 BCE-50 AD), the famous Roman encyclopedist, first described avulsions with a blunt hook, double ligation, venectomy and cautery to treat varicose veins[4]. The Roman surgeons did not use any form of anesthetics; one can imagine that this was a very unpleasant experience. The Roman surgeon and philosopher Claudius Galenum (129-200) used a hook to perform multiple short avulsions of varicose veins.

In Bizantine times, the physician Oribasius of Pergamum (325-405) devotes three chapters of his book *Synagogue Medicae* to the subject of varicose vein treatment[5]. Many of his recommendations are still valid:

- The surgeon should shave the leg and bathe the patient.
- When the patient is still warm from the bathe, the surgeon should stand up so that he is supported only by the varicosed leg and mark all of the swellings with small superficial incisions.
- After a incision on the highest part of the swelling, the surgeon should extract the varix by pulling it up with a cirsulce (hook). After the first incision and isolation of the varicosis, we continue with the remaining incisions.
- The main cirsotomy (removal of varisosity) starts from the lowest part of the leg upwards. When the varix is pulled up, the surgeon should cut all the varicose veins. Remove the veins, because if ligated, they can form new varicosities.

Paulus of Aegina, a Greek surgeon (607-690) described the main anatomy of varicose veins and recognized that ligation and removal of the great saphenous vein (GSV) was important[6]. In Arab medicine, treatment of varicose veins was dominated by cautery. However, the use of an rudimental external stripper was first reported by El Zahrawi (Albucasis de Cordova), a Muslim surgeon (936-1013)[7]. By the 13th century, a lot of progress was made in surgical procedures led by European physicians. The progress of surgery stalled for about 350 years, when barbers start to routinely conduct surgery.

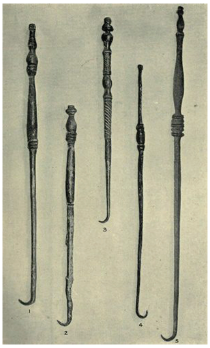


Figure 2.
Roman instruments

Amboise Paré, a famous surgeon in the Renaissance (1510-1590) modified the techniques of El-Zahrawi and definitively abandoned external cauterization of varicose veins to reintroduce their ligation[8]. He first described the ligation of the GSV in the groin. In these times , a detailed description of the venous system was made by Andreas Vesalius (1514-1564) and the presence of valves was demonstrated by Jeronimus Fabricius (1533-1619). Despite anatomical and physiological development, surgical treatment of varicose veins did not seem to be popular, as patients suffered gigantically during the operation.

The advent of anesthesia and antiseptic surgery rapidly advanced the treatment of varicose veins. Friedrich Trendelenburg, the most well-known venous surgeon (1841-1891), is associated with modern varicose vein surgery, when quoting "… the saphenous reflux must be the first step in control distal varicosities…”[9]. He made a 3 cm transverse incision at the junction of the middle and upper third of the thigh and ligated the GSV in situ[10]. Patients were hospitalized for 5 weeks. Trendelenburg recommended that this technique had to be applied only to those limbs in which compression tests, described by Brodie in 1846, revealed the incompetency of the saphenofemoral valve.

In 1896, William Moore, an Australian surgeon (1859-1927) suggested some modifications on Trendelenburg's publication[11,12]. The most important modification was ligation and division of the GSV just below the saphenofemoral junction. He presented a detailed account of the aetiology, pathophysiology and diagnosis of venous disease and reported excellent results after operation on 22 patients, mainly with leg ulcers. Moore routinely used elastic bandages in the postoperative period. In the same period, Thelwall Thomas (1865-1927) emphasized the importance of ligation and division of all branches at the saphenofemoral junction, the ‘crossectomy’.

Stripping of the saphenous veins was added to proximal ligation in the early twentieth century. William Keller (1874-1959) was the first to describe an internal stripper for stripping out the GSV in 1905[13]. The vein was removed by passing a rigid wire through the vein. At the distal end of the vein, the wire was tied with a ligature to extract the vein in an inverted way. A few year later, William Babcock (1872-1963) modified Keller's technique with the use of a flexible internal stripper with an acorn tip[14]. The ‘Babcock stripper’ can be regarded as the prototype of all strippers currently in use.

Short stripping and high ligation of the GSV has been the gold standard in the treatment of great saphenous varicose veins for many years. In 1952, the Seldinger technique was invented by Sven-Ivar Seldinger, a Swedish radiologist (1921-1998)[15]. This simple technique accelerated the development of endovenous techniques, as radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). The proposed benefits of endovenous techniques were to improve efficacy and health-related quality of life and to reduce complications, costs and postprocedural pain. Nowadays, these endovenous techniques are frequently compared in randomized studies.

Anatomy

The lower extremity venous system is a complicated and extremely variable network of connecting veins, which are classified according to their relationship to the muscular fascia. The deep veins lie beneath the muscular fascia and drain the lower extremity muscles. The superficial veins are located above the deep fascia and drain the cutaneous microcirculation, and the perforating veins that penetrate the muscular fascia connecting the deep and superficial veins. Although much thinner walled than arteries, veins are composed of intimal, medial and adventitial layers. The superficial, deep and most perforating veins contain bicuspid valves formed from folds of endothelium. Valves are most common in the distal leg and decrease towards the hip. In the lower extremities, the valves function to divide the hydrostatic column of blood into segments and ensure flow from superficial to deep and from caudal to cephalad[16].

The superficial venous system includes the reticular veins as well as the GSV and small saphenous vein (SSV) and their tributaries[17]. The GSV arises from the medial part of the dorsal pedal venous arch and ascends anterior to the medial malleolus, crossing the tibia at the junction of the distal and middle third of the calf to pass posteromedial to the knee. The vein then ascends medially in the thigh to perforate the deep fascia and join the common femoral vein 3-4 cm inferior and lateral to the pubic tubercle[18]. The saphenous nerve lies anterior to the great saphenous vein in the calf and may be injured by procedures extended into the calf.

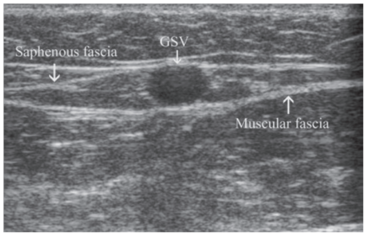


Figure 3.
The Egyptian eye

From the upper calf to the groin, the GSV is usually contained within an envelope of thin fascia, the muscular and saphenous (superficial) fascia[19]. Visualization of this fascial envelope is an important way of identifying the GSV with duplex ultrasound and has been described as having the appearance of an “Egyptian eye”. This fascial envelope often prevents the GSV from becoming significantly dilated, even when large volumes of reflux pass along its entire length. A normal GSV is typically 3-4 mm in diameter in the mid thigh. Just below the saphenofemoral junction, the GSV receives several additional important tributary veins, which is called “crosse”. These include the lateral and medial femoral cutaneous branches, the external circumflex iliac vein, the superficial epigastric vein, and the internal pudendal vein. These tributaries are frequently involved in the reflux that leads to the appearance of surface varicose veins on the lower thigh or upper calf. A valve is present at the saphenofemoral junction in 94-100% of persons, while the main trunk of the GSV contains at least six valves[20,21].

Superficial veins are also connected to a variable number of perforating veins that pass through openings in the muscular fascia to join directly with the deep veins of the calf or thigh. Perforating veins usually contain venous valves that prevent reflux of blood from the deep veins into the superficial system[21]. Numerous perforating veins can be divided into four groups of clinical significance: perforators of the foot, medial calf, lateral calf and thigh. Moreover, eponyms as perforators of Cockett and Boyd, should not be used. The small saphenous vein, or lesser saphenous vein arises from the dorsal pedal arch and ascends posterolaterally from behind the lateral malleolus to a variable termination in the popliteal vein. It usually lies directly on the muscular fascia till it enters the popliteal space. Approximately 60% of SSV's join the popliteal vein within 8 cm of the knee joint, 20% enter the GSV via anterior or posterior tributaries, 20% join the femoral or deep femoral vein[18]. A cranial extension of the SSV, often called Giacomini vein, may ascend posterior in the thigh. The sural nerve ascends immediately lateral to the SSV.

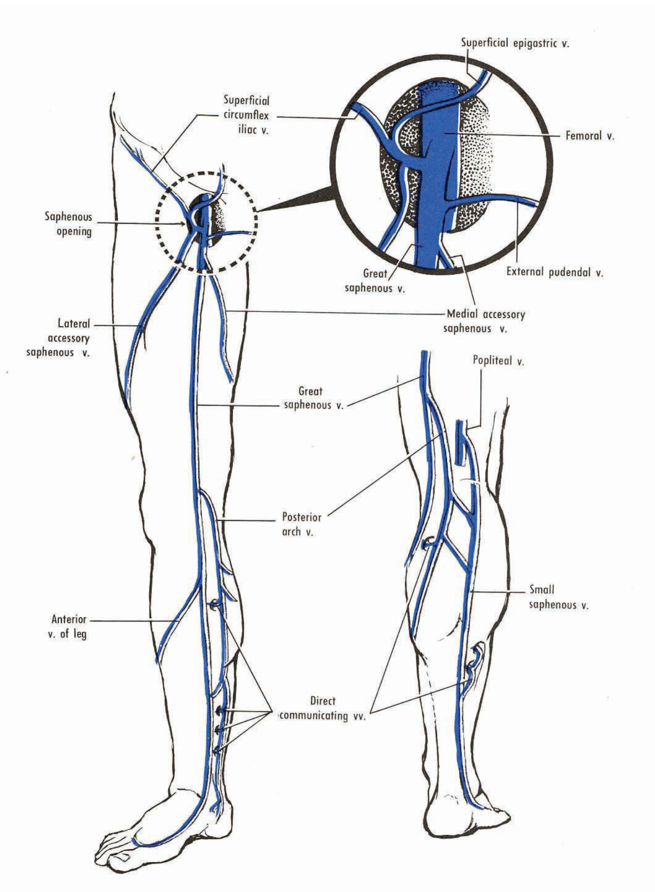


Figure 4. Venous anatomy of the lower limb

Chronic venous insufficiency

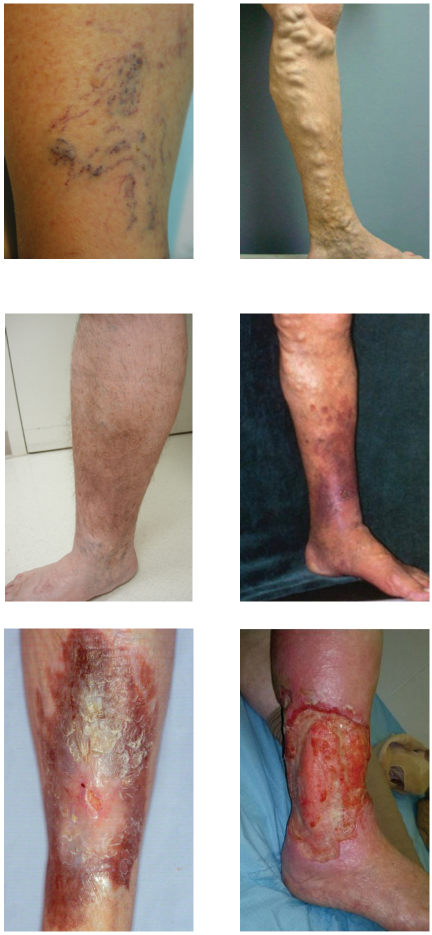
Chronic venous disease or insufficiency (CVI) is a term used to describe the changes that occur in peripheral tissue of the leg, due to prolonged high pressure in the veins. This condition causes a broad spectrum of symptoms including pain, swelling, edema, skin changes and ulceration. The most common manifestations of CVI are dilated cutaneous veins, such as teleangiectasias and reticular veins, and varicose veins. Although the term CVI is often used to exclude uncomplicated varicose veins, varicose veins have incompetent valves with increased venous pressure leading to progressive dilatation and tortuosity. Therefore, CVI represents the full spectrum of manifestations of chronic venous disease.

The CEAP classification system provides a mechanism for the uniform diagnosis of chronic venous disease and comparison of patient populations. The four components of the CEAP classification are a description of the clinical disease class based upon objective signs (C), the etiology (E), the anatomic distribution of reflux and obstruction (A), and the underlying pathophysiology, whether related to reflux or obstruction (P)[22].

Varicose veins have an estimated prevalence between 5-30% in the adult population, with a female to male predominance of 3 to 1, although a more recent study supports a higher male prevalence[23]. The Edinburgh Vein Study screened 1566 subjects with duplex ultrasound for reflux finding CVI in 9.4% of men and 6.6% of women after age adjustment. The prevalence of CVI correlated closely with age and sex, being 21.2% in men >50 years and 12% in women >50 years[24]. Another epidemiological study was performed in Bonn, Germany among 3072 participants[25]. Only 9.6% of the population showed no signs of venous disorders, according the CEAP classification. A pathological reflux in the superficial venous system was found in 21.0%, predominantly affecting the GSV. Six years after this study, the participants were reinvestigated, showing a high incidence of progression to higher C-classes[26]. CVI has a substantial negative impact on quality of life, primarily affecting physical and emotional items in mild disease. From the appearance of edema, quality of life shows a similar pattern to patients suffering diabetes and cancer, and even worsens with advanced CVI[27].

Table 1. The CEAP classification with illustrations of C stages

Clinical	
C0	No clinical signs
C1	Reticular veins, teleangiectasias
C2	Varicose veins
C3	Edema
C4	Skin changes without ulceration a. pigmentation, dermatitis, eczema b. lipodermatosclerosis
C5	Skin changes with healed ulceration
C6	Skin changes with active ulceration
Etiology	
Ec	Congenital
Ep	Primary
Es	Secondary
Anatomy	
As	Superficial veins
Ad	Deep veins
Ap	Perforating veins
Pathophysiology	
Pr	Reflux
Po	Obstruction



Mechanochemical endovenous ablation

The introduction of minimal invasive techniques in the late 1990's, changed the landscape of varicose vein treatment. Several prospective clinical studies on EVLA and RFA established the safety and efficacy of these procedures[28,29]. The first randomized clinical trial comparing EVLA with saphenofemoral ligation and stripping was only published in 2007[30]. However, endothermal techniques require the use of tumescent anesthesia to neutralize the heat produced during treatment. Tumescent anesthesia is associated with patient discomfort and is a time consuming step in endothermal procedures. Also, heat related complications, like skinburn, paresthesia and prolonged postprocedural pain are described despite the use of tumescent anesthesia.

Searching for new techniques to minimize the negative effects of endothermal ablation, a method to occlude varicose veins in a mechanochemical way was introduced. The ClariVein® system was developed in 2005 by the radiologist Michael Tal from Yale University to the analogy of a washing machine[31]. Animal studies were performed to provide proof of concept with excellent results[32]. The combination of mechanical ablation and liquid sclerotherapy provided 100% occlusion of the treated veins after 84 days.

The ClariVein® infusion catheter was introduced by *Vascular Insights LLC* (Madison, CT, US). In May 2008, it gained clearance from the US Food and Drug Administration (FDA) for the indication of infusion of physician-specified agents in the peripheral vasculature. ClariVein® obtained the CE mark in May 2010, allowing the use in Europe (CE 558723). The first clinical trial was performed at Englewood Hospital, New Jersey by the vascular surgeon, Steve Elias[33].

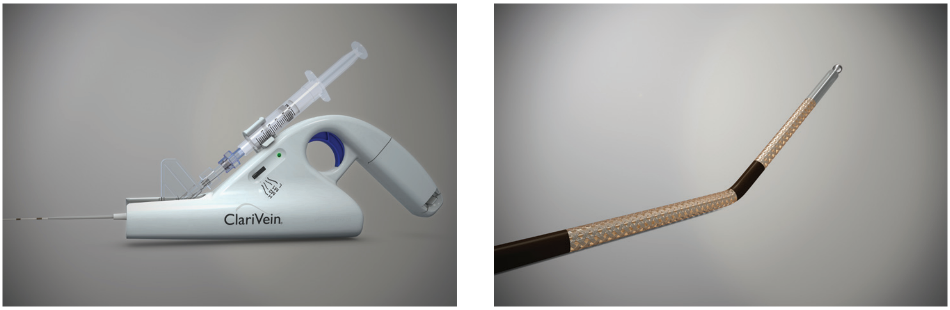


Figure 5. The ClariVein® system. Used with permission of Vascular Insights LLC

Mechanochemical endovenous ablation (MOCA) combines mechanical damage using a rotating wire to the endothelial layer with the infusion of a liquid sclerosant. The aim of the mechanical action is fourfold: (1) promoting the coagulation activation by damaging the endothelium, (2) inducing a vasospasm reducing the vein diameter, (3) increasing the action of sclerosant, and (4) ensuring an even distribution of the sclerosant. The liquid sclerosant then produces irreversible damage to the cellular membranes of the endothelium, resulting in fibrosis of the vein. MOCA using the ClariVein® system has several advantages compared with other endothermal techniques, through the exclusion of thermal energy. These advantages include the omission of tumescent anesthesia, no risk of thermal injury to the surrounding tissue, as skin, muscle and nerves, and reducing procedural and postprocedural pain.

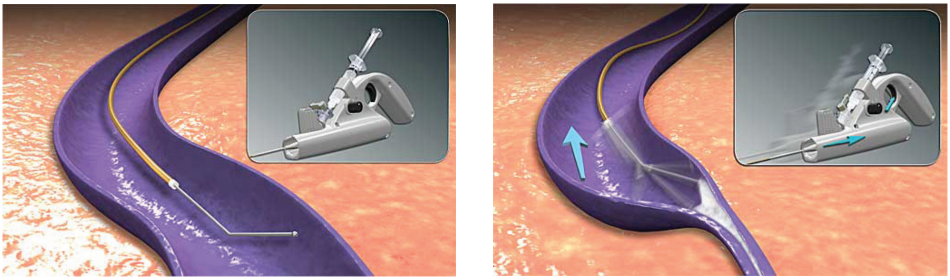


Figure 5. The ClariVein® system. Used with permission of Vascular Insights LLC

Aim and outline of this thesis

The work described in this thesis is based on the collaboration between the Departments of Vascular Surgery in the Rijnstate Hospital, Arnhem and St Antonius Hospital, Nieuwegein, The Netherlands. The general aim of this thesis was to study the safety and outcome of mechanochemical endovenous ablation in the treatment of varicose veins.

In the last decades, the introduction of minimally invasive endovenous techniques, including endovenous laser ablation, radiofrequency ablation and ultrasound foam sclerosis, has resulted in almost abandonment of the 'gold standard' high ligation, with or without surgical stripping. For a general update, we performed an extensive review on all current endovenous treatment modalities for varicose veins. **Chapter 2** focuses on developments in technique, mechanisms of action, outcome and complications of those treatment modalities.

Before the administration of the ClariVein® system, we designed the first European study for MOCA using polidocanol in patients with GSV incompetence. This safety study with favorable results, presented in **Chapter 3**, was the point of departure for our study group to start new studies evaluating the outcome of MOCA in larger groups. In 2008 the ClariVein® system was approved by the FDA, and a prospective cohort of patients with incompetent great and small saphenous veins vein were treated with MOCA. **Chapter 4** reveals the six-weeks and one-year anatomical results of 50 patients treated for small saphenous vein incompetence with a specific focus on differences in used polidocanol concentration.

After the safety study, a prospective multicenter registry study was initiated. As MOCA is a novel treatment modality, adjustments in the technique were made during study group meetings, when analyzed results of our study pointed out clear indications that would lead to improvement of technique. One hundred-and-six consecutive patients with GSV incompetence were treated using polidocanol 2% in the proximal vein and polidocanol 1.5% in the remaining segment. In **Chapter 5**, we present the clinical and anatomical results after one-year follow-up. Also, postprocedural pain and quality of life were evaluated.

Simultaneously, based upon the assertion that MOCA eliminates thermal damage, postprocedural pain after MOCA and radiofrequency ablation was studied in a subgroup of patients of the prospective registry study and consecutive patients undergoing radiofrequency ablation. The results of this study are presented in **Chapter 6**.

Conclusions of previous studies on MOCA are supporting the therapeutic effect of varicose vein ablation on a mechanochemical way. As a consequence, we designed a randomized controlled multicenter trial that compares the treatment of GSV incompetence with MOCA and radiofrequency ablation. The study protocol for this ongoing MARADONA trial is described in **Chapter 7**.

Chapter 8 focuses on histopathological changes of a vein treated with MOCA.

Finally, the main findings of this thesis are summarized in **Chapter 9** followed by a general discussion. **Chapter 10** provides a Dutch version of the summary.

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